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(71) Applicant: 000003001
Teijin Co. Ltd.
Osaka-fu, Osaka-shi, Chuo-ku, Minami-honmachi 1-6-7

(72) Inventor: Mr. Sasano, c/o Teijin Co. Ltd. Tokyo Research Centre,
Tokyo-to, Hino-shi, Asahigaoka 4-3-2

(72) Inventor: Mr. Makino, c/o Teijin Co. Ltd. Tokyo Research Centre,
Tokyo-to, Hino-shi, Asahigaoka 4-3-2

(72) Inventor: Mr. Suzuki, c/o Teijin Co. Ltd. Tokyo Research Centre,
Tokyo-to, Hino-shi, Asahigaoka 4-3-2

(74) Agent: Mr. Maeda (attorney)

# (54) Title of the Invention: Granular Calcium Composition and a Tablet Made up of the Same

## (57) Abstract

**Aim** To provide a calcium preparation with high compliance [the English word is used in the Japanese original] in taking [as medication] and good mouldability.

**Construction** A granular calcium composition comprising a calcium compound such as anhydrous calcium hydrogenphosphate or calcium carbonate and 1-15wt% of polyvinyl pyrrolidone relative to the calcium compound, wherein the average particle diameter of 60wt% or more of the granular composition is 37μm or more.

## Claims

**Claim 1** A granular calcium composition comprising one or two or more calcium compounds selected from the group consisting of anhydrous calcium hydrogenphosphate, calcium hydrogenphosphate dihydrate, calcium dihydrogen phosphate monohydrate, calcium carbonate, calcium lactate, calcium glucuronate, calcium glycerophosphate, and calcium L-aspartate and 1-15wt% of polyvinyl pyrrolidone relative to said calcium compound, wherein the particle diameter of 60wt% or more of said granular calcium composition is 37μm or more.

**Claim 2** A tablet comprising the granular calcium composition of Claim 1.

**Claim 3** A tablet according to Claim 2, wherein 60wt% or more of said tablet is said granular calcium composition.

## Detailed Description of the Invention

0001 **Field of Industrial Application**

The present invention relates to a novel granular calcium composition and a tablet containing the same.

0002 More particularly, the present invention relates to a granular calcium composition and a tablet containing the same in which the texture when chewed in the mouth is improved and which can be used for supplying calcium.

0003 **Prior Art**

Compounds containing calcium are administered orally to supply calcium to promote the development of the bones and teeth of those who are delicate or have a weak constitution or to prevent brittleness of the bones or teeth in pregnant or lactating women. Anhydrous calcium hydrogenphosphate, calcium hydrogenphosphate dihydrate, calcium dihydrogen phosphate monohydrate, calcium carbonate, calcium lactate, calcium glucuronate, calcium glycerophosphate, calcium L-aspartate, etc can be cited as such calcium-containing compounds.

0004 These compounds are normally moulded into tablets or granules, powders, etc together with excipients, colouring matter, fragrances, etc , but in order to increase compliance it is important that the dosage form should be easy to take, since the majority of those who it is intended should take it are children, women, or elderly persons.

0005 **Problems to be Solved by the Invention**

However, with any of anhydrous calcium hydrogenphosphate, calcium hydrogenphosphate dihydrate, calcium dihydrogen phosphate monohydrate, calcium carbonate, calcium lactate, calcium glucuronate, calcium glycerophosphate, and calcium L-aspartate, at the normal particle diameter (particles of the particle diameter range normally required for moulding into tablets, granules, etc), that is to say, with particles of which 80wt% have a particle diameter of 37μm or more, complete minute disintegration in the mouth at the time of chewing does not occur, and as a result a floury or rough texture remains, and the sensation when taking cannot be called adequate. A number of measures have therefore been devised to solve this problem.

0006 The first is a method in which, leaving the particle diameter of such calcium compounds in a range where 80wt% is 37μm or more and less than 200μm, in other words not doing anything to such calcium compounds themselves, the material is diluted with other components with high solubility, for example sugars such as mannitol, and then moulded into tablets or granules. The "flouriness" of the calcium component is diluted and improved by the sugar, etc, but the quantity of excipient of course increased relative to a fixed quantity of calcium, so that an increase in the size or number of the pills or an increase in the total quantity of the granules, etc has been unavoidable.

0007 The second is a method in which the particle diameter of the calcium compound granules is made smaller. If the powder of these calcium compounds which is normally used for preparations, of which 80wt% is in the range [of sizes which are] 37μm or more and less than 200μm, is ground such that 90wt% falls within the range [of sizes which

are] 37μm or less using a pulverizer etc, the "flouriness" is almost eliminated. However, as a result of such "fine-powdering", the fluidity and the ability to bind of these calcium compounds is reduced and even if, for example, it could be moulded into tablets, these tablets are of low mechanical strength, low in hardness and easily chipped.

0008 There is therefore, a demand for a method which simultaneously eliminates any increase in tablet size, increase in tablet number, or increase in the quantity of granules, and any impairment of mouldability. That is to say, there is a demand for a method which improves the texture [experienced] at the time of chewing while keeping the percentage by weight of the calcium compound in one dosage unit (for example, one tablet or one wrapper) of the preparation comparatively high.

0009 **Means of Solving the Problems**

As a result of thorough research into these problems of the prior art, the present inventors discovered that, surprisingly, with a granular composition made up of a certain type of calcium compound and 1-15wt% of polyvinyl pyrrolidone relative to the calcium compound, rapid disintegration is found, only if the average particle diameter of the granular composition is caused to be [in] a fixed range, and as a result the texture in the mouth when chewing [it] is good.

0010 Thus, the present invention is a granular calcium composition made up of one or two or more calcium compounds selected from the group consisting of anhydrous calcium hydrogenphosphate, calcium hydrogenphosphate dihydrate, calcium dihydrogen phosphate monohydrate, calcium carbonate, calcium lactate, calcium glucuronate, calcium glycerophosphate, and calcium L-aspartate, and 1-15wt% of polyvinyl pyrrolidone relative to the calcium compound, and in which 60wt% or more of the granular calcium composition has a particle diameter of 37μm or more, and a tablet made up of this granular calcium composition.

0011 In the present invention one or two or more selected from the group consisting of anhydrous calcium hydrogenphosphate, calcium hydrogenphosphate dihydrate, calcium dihydrogen phosphate monohydrate, calcium carbonate, calcium lactate, calcium glucuronate, calcium L-aspartate, and calcium glycerophosphate are used as calcium compounds. Of these, anhydrous calcium hydrogenphosphate, calcium carbonate, and calcium lactate are preferable, and anhydrous calcium hydrogenphosphate is particularly preferable.

0012 "Polyvinyl pyrrolidone of the present invention" signifies ones that are normally used as binders for drugs; ones with an average molecular weight from 10,000 to 1,200,000 can be cited as examples.

0013 The quantity of this polyvinyl pyrrolidone is 1-15wt% relative to the calcium compound. With less than 1wt% the binding strength is weak and granulation cannot be achieved, while if it exceeds 15wt% enormous lumps are generated and it is difficult to obtain suitable granules. Within [the above range], 3-10wt% is preferable as the quantity of polyvinyl pyrrolidone.

0014 The granular composition of the present invention is a granular calcium composition made up of the above calcium compounds and polyvinyl pyrrolidone, and this granular calcium composition can be manufactured by the following methods, for example.

0015 It is desirable that, before it is granulated, the above calcium compound for use in the present invention be finely powdered such that 80wt% or more has a particle diameter of less than 37μm. With regard to the fine-powdering, [it] should be pulverized in a normal pulverizer, for example a hammer mill. Next, the finely-powdered calcium compound is mixed uniformly with polyvinyl pyrrolidone. With regard to the particle diameter of the polyvinyl pyrrolidone in this case, it is desirable that 90wt% or more of the whole be in a particle size distribution of less than 250μm.

0016 With regard to the mixer, it is preferable from the viewpoint of yield that [mixing] be carried out with the same apparatus as the granulation process described later, and normally a fluidized-bed granulat[or]-dryer or a high-speed mix[er]-stir[rer]-granulator is used. Inside the apparatus, water is sprayed onto the mixture of the uniformly mixed and stirred calcium compound and polyvinyl pyrrolidone, and [the mixture] is granulated into a granular composition. With regard to the above [processes], they are carried out under [the following] conditions: normally the uniformly mixed mixture of calcium compound and polyvinyl pyrrolidone is taken into the apparatus, about 10wt% of water relative to it is sprayed at a rate of 20ml/minute, and when the whole amount has been sprayed, the granulated substance is dried until the temperature of the exhaust air [*or* "exhaust gas"] in the apparatus exceeds 40°C. Next, the granular composition obtained is passed through a 350μm-opening sieve, after which a granular calcium composition is obtained of which 60% or more has a particle diameter of 37μm or more when the particle size distribution is measured with an electromagnetic micro "sieve shaker" (manufactured by Tsutsui Rikagaku Kikai).

0017 The granular calcium composition thus provided by the present invention is provided in that form as a calcium compound granular preparation (granules) with pre-chewing flouriness eliminated and hardness improved. In this case, a small amount of a flavouring agent or a corrective may be added to correct the taste [and/or] smell of the granules.

0018 In addition, making into tablets by tableting the granular calcium composition thus provided together with a disintegrator, lubricant, flavouring agent, corrective, etc is included as a mode of the present invention. In this case it is preferable that the quantity of components other than the granular calcium composition be as small as possible, normally 40% or less, and more preferable that it be 30% or less.

0019 In addition, moulding of tablets with a hardness of 4.0kg or more is normally preferable in order to maintain their mechanical properties as tablets.

0020 Thus, with the present invention the calcium compound content is large, the mechanical strength is adequate, and flouriness, hardness, etc are not experienced when chewing: in short, due to the provision of calcium compound granules or tablets with improved texture in the mouth, and the fact that an improvement in compliance as a calcium supplement can be expected, [it] has the potential to contribute greatly to medical treatment.

0021 **Embodiments**

The present invention will now be explained in more detail with reference to embodiments, but the present invention is not limited to these.

0022 **Embodiment 1 and Comparative Examples 1-6**

665g of fine powder anhydrous calcium hydrogenphosphate (standard item manufactured by Kyowa Kagaku Kogyo: particle size distribution 16.3% 37μm or more, 83.7% less than 37μm) and 35g of polyvinyl pyrrolidone (manufactured by BASF Co, Kollidon K-30) were taken, placed in a fluidized bed granulator, and mixed uniformly by an airflow. Next, while about 10wt% of water relative to this uniform mixture was sprayed at a rate of 20ml/minute, granulation was performed, after which granular anhydrous calcium hydrogenphosphate of the present invention was obtained by further drying until the temperature of the exhaust air inside the apparatus exceeded 40°C (Embodiment 1). The particle size distribution of the obtained granules was 68.5% 37μm or more, and 31.5% less than 37μm.

0023 At the same time, for comparison, the various binders in Table 1 were taken and granules were obtained by performing granulation in the same way as in Embodiment 1 (Comparative Examples 1-6). Note: a commercial product (Rikamitto [*another of many*

*possible transliterations would be* "Liquamit"] (registered trademark) U-100, manufactured by Kyowa Kagaku Kogyo) was used in Comparative Example 1.

0024 The particle size distribution of the obtained granules and the results of testing of texture when chewed by 20 volunteers for Embodiment 1 and Comparative Examples 1-6 are given in Table 1.

0025 Table 1

| granules | | particle size distribution | texture when chewed (20 persons) | |
|---|---|---|---|---|
| No. | binder | | felt it was floury | felt it was not floury |
| Embod. 1 | polyvinyl pyrrolidone (5wt%) | 150μm residue 31.9%<br>150-75μm 20.8%<br>75-37μm 15.8%<br>passing through 37μm 31.5% | 0 persons | 20 persons |
| Comp.Ex. 1 | sodium polyacrylate (0.17wt%) | 150μm residue 0.0%<br>150-75μm 8.5%<br>75-37μm 51.5%<br>passing through 37μm 40.0% | 18 persons | 2 persons |
| Comp.Ex. 2 | sodium polyacrylate (1wt%) | 150μm residue 15.0%<br>150-75μm 30.0%<br>75-37μm 33.5%<br>passing through 37μm 21.5% | 20 persons | 0 persons |
| Comp.Ex. 3 | potato starch (5wt%) | 150μm residue 5.0%<br>150-75μm 10.5%<br>75-37μm 35.6%<br>passing through 37μm 48.9% | 16 persons | 4 persons |
| Comp.Ex. 4 | hydroxy propyl cellulose (5wt%) | enormous lumps were generated at the time of granulation, and suitable granules could not be obtained. | - | - |
| Comp.Ex. 5 | "Macro Goal 6,000"[?] (5wt%) | 150μm residue 20.5%<br>150-75μm 13.5%<br>75-37μm 25.4%<br>passing through 37μm 40.6% | 10 persons | 10 persons |
| Comp.Ex. 6 | gum arabic (5wt%) | 150μm residue 25.0%<br>150-75μm 20.3%<br>75-37μm 30.5%<br>passing through 37μm 24.2% | 15 persons | 5 persons |

" - " in the table indicates that testing was not performed

0026 It can be seen from Table 1 that when polyvinyl pyrrolidone is used as a binder, granules with an excellent texture in which flouriness is not experienced are obtained, while with the other commonly used binders, no granules were obtained, or only granules with an inferior texture in which flouriness was experienced were obtained.

0027 **Embodiments 2-4 and Comparative Examples 7-10**

Granulation was performed by the same method as Embodiment 1, taking fine powder anhydrous calcium hydrogenphosphate (standard item manufactured by Kyowa Kagaku Kogyo) as in Embodiment 1, and varying the quantity of polyvinyl pyrrolidone (manufactured by BASF Co, Kollidon K-30) as shown in Table 2. The particle size distribution of the obtained granules and the results of testing of texture when chewed by 20 volunteers are shown in Table 2.

0028 Table 2

| granules | quantity of polyvinyl pyrrolidone (wt%) | particle size distribution | texture when chewed (20 persons) | |
|---|---|---|---|---|
| | | | felt it was floury | felt it was not floury |
| Comp.Ex. 7 | 0.1 | granulation difficult | - | - |
| Comp.Ex. 8 | 0.5 | ,, | - | - |
| Embod. 2 | 1 | 150μm residue 20.8%<br>150-75μm 15.4%<br>75-37μm 28.3%<br>passing through 37μm 35.5% | 0 persons | 20 persons |
| Embod. 3 | 10 | 150μm residue 28.6%<br>150-75μm 25.5%<br>75-37μm 20.3%<br>passing through 37μm 25.6% | 1 person | 19 persons |
| Embod. 4 | 15 | 150μm residue 20.0%<br>150-75μm 15.3%<br>75-37μm 30.1%<br>passing through 37μm 34.6% | 3 persons | 17 persons |
| Comp.Ex. 9 | 20 | enormous lumps appeared at the time of granulation and granules could not be obtained | - | - |
| Comp.Ex. 10 | 25 | ,, | - | - |

" - " in the table indicates that testing was not performed

0029 It can be seen from Table 2 that when the quantity of polyvinyl pyrrolidone is 1-15wt% granules with a excellent texture can be manufactured, but with less than 1wt% granulation cannot be performed, and when 15wt% is exceeded enormous lumps are generated and suitable granules are not be obtained.

0030 **Embodiment 5**

Tablets were manufactured by the following method, using granules manufactured in Embodiment 1 (Embodiment 5).

| | |
|---|---|
| Granular anhydrous calcium hydrogenphosphate | 72.0% |
| D-sorbitol | 10.0% |
| D-mannitol | 16.8% |
| Flavour | 0.2% |
| Magnesium stearate | 1.0% |

0031 In the above formula, with a "mortar-pestle" [*sic*] of 10mm diameter tablets of 500mg weight were manufactured in an Elwecker [?-*or* "Erueca"] single punch tableting machine. The average hardness (n=20) of the obtained tablets was 5.2kg.

0032 Next, the texture when these tablets were chewed was investigated with 20 volunteers: the results are shown in Table 3.

0033 For comparison, tablets (Comparative Example 11) were moulded by the same method as above, using a commercial product in which sodium polyacrylate was used as a binder instead of polyvinyl pyrrolidone (Comparative Example 1). The average hardness of these tablets was 5.0kg. The texture when these tablets were chewed was also investigated with 20 volunteers as above: the results are shown in Table 3.

0034 Table 3

| tablet (binder) | texture when chewed (20 persons) | |
|---|---|---|
| | felt it was floury | felt it was not floury |
| Embodiment 5 (polyvinyl pyrrolidone 5wt%) | 0 persons | 20 persons |
| Comp. Example 11 (sodium polyacrylate 0.17wt%) | 19 persons | 1 person |

0035 It can be seen from Table 3 that the texture before[*sic*] chewing of the tablets of the present invention shows a marked improvement.

0036 **Embodiment 6**

1wt% of magnesium stearate was mixed with granules manufactured in Embodiment 1, after which, with a "mechanical mortar" of 10mm diameter, tablets of 500mg weight were manufactured in an Elwecker [? Or "Erueca"] single punchtableting machine.

0037 When the texture when these tablets were chewed was investigated with 20 volunteers, not one made any complaint about any texture deficiency such as flouriness.

***Translator's General Note: The Japanese text generally makes no distinction between singular and plural, and therefore most singulars and plurals in the English translation are based on deduction from context. The same applies to "a" and "the".***